

**REMARKS****I. Overview**

Applicant's have reviewed and considered the Final Office Action dated December 22, 2005, the references cited therewith, and the advisory action of April 4, 2006. Applicants believe that the following supplemental after final amendment alleviates the Examiner's concerns and is responsive to each rejection of record, including the those presented in paragraphs 14-28 and 37-42.

Claims 1-11, 15, 18-25, 29-73 and 76-80 are pending in the present application. Claims 48-67 have been canceled in order to expedite prosecution. Claims 1, 10, 24, 36, 38, 40, and 76-80 have been amended. Support for the amendments can be found in the Published Specification at paragraphs 8, 43, 103-04, 112 and 114-115. The present response is an earnest effort to place all claims in proper form for immediate allowance. Reconsideration and passage to issuance is therefore respectfully requested.

**I A. Rejections presented in paragraphs 14-28 and 37-42**

A. Claims 1, 10, 24, 36, 38, 40, 79 and 80 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention with respect to the phrase "wherein at least one of the RER sites is recognized by a Type IIS restriction enzyme".

In order to expedite prosecution, Applicants have amended the claims 1, 10, 24, 36, 38, 40, 79 and 80 to remove the phrase "at least" so that they now recite "wherein one of the RER sites is recognized by a Type IIS restriction enzyme". Applicants respectfully submit that claims 1, 10, 24, 36, 38, 40, 79 and 80 are in a form for immediate allowance.

B. Claims 10, 11, 15, and 18-25, 29-35, 38-41, and 44-47 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention with respect to the phrase "subjecting the cDNA to a Type IIS restriction enzyme that recognizes one Type IIS RER site located at the 5' end of the marker exon and cleaving the cDNA upstream of the 5' end of the marker exon".

Claim 10 has been amended to remove the phrase "one Type IIS RER site" so that it now recites "the Type IIS RER site". Claims 24, 38 and 40 have been similarly amended. Applicants respectfully submit that claims 10, 11, 15, and 18-25, 29-35, 38-41, and 44-47 are in a form for immediate allowance.

C. Claims 36, 37, 42 and 43 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention with respect to the phrase "RNA tags".

Claim 36 has been amended to remove the phrase "RNA tags" so that it now recites "nucleotide sequence tags". Applicants respectfully submit that claims 36, 37, 42 and 43 are in a form for immediate allowance.

D. Claims 76-80 stand rejected for insufficient antecedent basis for "isolating said RNA" and "reverse transcribing the isolated mRNA".

Claim 76 has been amended to remove the phrase "isolating said RNA" so that it now recites "isolating mRNA". Applicants respectfully submit that claims 76-80 are in a form for immediate allowance.

E. Claims 76-77 and 79 stand rejected for insufficient antecedent basis for "the first Type IIS restriction enzymes".

Claim 76 has been amended to remove the phrase "the first Type IIS restriction enzymes" so that it now recites "recognized by Type IIS restriction enzymes". Applicants respectfully submit that claims 76-77 and 79 are in a form for immediate allowance.

## **II. Specification**

The Examiner writes that the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, specifically at pages 18 and 31 of the application. Accordingly, Applicants have amended the application so that it no longer reads <http://www.ncbi.nlm.nih.gov/>.

## **III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph**

The Examiner writes that claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner writes that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor at the time the application was filed had possession of the claimed invention. The Examiner writes that this is a new matter rejection necessitated by the amendment to the claims.

A. The Examiner writes that claim 1 has been amended to recite "subjecting said cDNA fragment to a DNA polymerase and nucleotides to generate a blunt-ended fragment". The Examiner writes that the specification lacks literal support for this limitation in the claim.

Applicants thank the Examiner for pointing out this inadvertent oversight. Accordingly, claim 1 has been amended to recite "subjecting said cDNA fragment to a Klenow enzyme and nucleotides to generate a blunt-ended fragment" as provided in the Published Specification, at

paragraph 114. In light of the above, Applicants respectfully request that this rejection be withdrawn and submit that claims 1-9 are in form for allowance.

B. The Examiner writes that claim 79 recites, at the bottom of page 30, cutting to "generate sequence tags of at least 8 nucleotides". The Examiner writes as claimed, this encompasses cleaving to generate any tag of any length greater than 8 nucleotides, including tags of 30, 40, 60, 100, and 1000 nucleotides. The Examiner writes the specification does not provide a structural basis for any enzyme that could cleave DNA and leave a tag of any greater than 20 nucleotides. The Examiner writes thus it would be remedial to replace "at least 8 nucleotides" with 8 to 20 nucleotides.

Applicants thank the Examiner for the recommended language and have adopted Examiner's suggestion so that claim 79 now recites "generate sequence tags of 8 to 20 nucleotides". In light of the above, Applicants respectfully request that this rejection be withdrawn and submit that claim 79 is in form for allowance.

#### **IV. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph**

Claims 10, 11, 15, 18-25, 29-47, and 76-80 stand rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The Examiner writes that this is an existing rejection, however, it is newly applied to newly entered claims 76-80.

A. The Examiner says that the omitted steps are for claims 36, 76, 77, and 79 and that a step is missing prior to the step of "self-ligating the cDNA fragment." As a type IIS restriction enzyme cuts outside of the non-palindromic recognition site and generally cuts leaving an overhang, the nature of the overhang is unknown. As the construct is specifically designed to

cut within the unidentified, adjacent exons, it is highly unlikely that the two overhangs would have compatible cohesive ends. To successfully achieve self-ligation, the unidentified cohesive ends must first be filled in to create blunt ends. The Examiner writes that only after this step would self-ligation even be possible.

Claims 36, 76, 77, and 79 have been amended so that they now recite "subjecting said cDNA fragment to a Klenow enzyme and nucleotides to generate a blunt-ended fragment". Support for this amendment can be found in the Published Specification at paragraph 114. In light of the above, Applicants respectfully request that this rejection be withdrawn and submit that claims 36, 76, 77, and 79 are in form for allowance.

B. Regarding claims 10, 24, 38, 40, 78 and 80, the Examiner writes that these claims lack essential elements pertaining to the linkers to be ligated to the type IIs cleaved fragments. The Examiner writes that for the practice of the invention, it is essential that the linkers comprise an appropriate number of randomized overhang nucleotides to allow for ligation of the linkers to the unidentified overhangs produced by the type IIs enzymes. The Examiner writes that again, as the type IIs restriction enzyme cleaves the cDNA in a region with unknown sequence and type IIs enzymes tend to leave an overhang, that in this case, the sequence of which would be unknown, it is necessary to account for the lack of a blunt end. The Examiner writes that in order to successfully ligate linkers onto the unknown cDNA tag end, the randomized overhang is a requirement.

Claims 10, 24, 38, 40, 78 and 80 have been amended so that they now recite "and portions of downstream cellular tags with a 5' single-stranded overhang; ligating a linker to the cDNA fragment, wherein said linker contains a 3' single-stranded overhang ligatable to said 5' single-stranded overhang of the exon tags of said cDNA fragment". Support for this amendment

can be found in the published specification at paragraph 115. In the event that the Examiner finds the language unacceptable, Applicants would welcome discussions with the Examiner regarding alternative acceptable terms equally defined by the disclosure. In light of the above, Applicants respectfully request that this rejection be withdrawn and submit that claims 10, 24, 28, 40, 78 and 80 are in form for allowance.

**V. Claim Rejections Under 35 U.S.C. § 102**

The Examiner writes that provisional application 60/458,152 provides support for SAVI, but does not provide support for the present incarnation of 5' SAVI or 3' SAVI. As such, all claims regarding 5' and 3' SAVI are treated as having the priority date of the instant application, i.e., March 26, 2004.

Claims 24, 25, 29-35, 40, 41, 46-54, 62-66, 68-73 and 80 stand rejected under 35 U.S.C. § 102(a) and under 35 U.S.C. § 102(e) as being anticipated by Pruitt (US 2003/0143578, of record). Applicants do not admit that Pruitt (US 2003/0143578) is prior art, and reserve the right to swear behind it at a later date. Claims 48-54 and 62-66 have been canceled in order to expedite prosecution.

Applicants do not concede that this application is not entitled to priority back to its provisional filing date and since Applicants believe the Pruitt reference is easily distinguished, Applicants respectfully submit that the claims are distinguishable over Pruitt (US 2003/0143578) for the reasons argued below. These arguments are presented in direct response to the Examiner's rejection where he provides for the first time that the present invention is not patentable because it is anticipated by Pruitt.

Applicants traverse this rejection as applied to claims 24 and 40. Pruitt does not teach each and every element of claims 24 and 40. Amended claim 24 recites “wherein the exon marker sequence comprises in a 5' to 3' direction ... two restriction enzyme recognition (RER) sites located at the 5' end of the marker exon, ... wherein one of the RER sites is recognized by a Type IIS restriction enzyme ... and two restriction enzyme recognition (RER) sites located at the 3' end of the marker exon ... wherein one of the RER sites is recognized by a Type IIS restriction enzyme”. Claim 40 recites similar elements as claim 24.

The present inventors teach that once the exon marker is integrated into the cellular genome an mRNA containing the marker exon is produced. The mRNA is ultimately reverse transcribed into cDNA and subjected to digestion with a Type IIS restriction enzyme (or enzymes) that recognize and cleave each of the first and second Type IIS RER sites located at each end of the marker exon, thereby producing a cDNA fragment that includes the marker exon and portions of the upstream and downstream cellular exon sequences (exon tags). Published Specification, at paragraph 74. The third and fourth restriction enzyme recognition sites in the marker exon allow for the marker exon to be cleaved out of amplified cDNA, facilitating the isolation of the exon tags. Published Specification, at paragraph 78.

In contrast, Pruitt (US 2003/0143578) describes at paragraph 43 the elements of its gene-trap vector as comprising a recombinogenic sequence element such as *frt*, a splice acceptor sequence, a type IIS restriction endonuclease site, a recombinogenic sequence, a type IIS restriction endonuclease site, and a splice donor sequence. Pruitt teaches at paragraph 43 that the inclusion of a reporter or selection sequence is optional. Furthermore, Pruitt does not teach a marker sequence containing at least two restriction enzyme recognition (RER) sites, where one is a Type IIS restriction enzyme recognition (RER) site. Rather, Pruitt teaches in Figure 1A,

restriction enzyme recognition sequences located outside of the marker sequence. Thus, Pruitt does not teach the identical invention in as complete detail as is contained the claim and therefore cannot anticipate claim 24. MPEP § 2131.

In light of the above, Applicants respectfully submit that 24 is not anticipated by Pruitt. Likewise, claims 25, 29-35 depending from claim 24 are not anticipated for the reasons argued above plus the elements in the claims.

Independent claim 40 and dependent claims 41, 46-47 recite similar elements as claim 40 and are not anticipated by Pruitt for the reasons argued above plus the elements in the claims.

Independent claim 68 and dependent claim 69 recite similar elements as claim 68 and are not anticipated by Pruitt for the reasons argued above plus the elements in the claims.

Independent claim 70 and dependent claim 71 recite similar elements as claim 70 and are not anticipated by Pruitt for the reasons argued above plus the elements in the claims.

Independent claim 72 and dependent claim 73 recite similar elements as claim 72 and are not anticipated by Pruitt for the reasons argued above plus the elements in the claims.

Independent claim 80 is not anticipated by Pruitt for the reasons argued above plus the elements in the claims. Applicants believe they have overcome the §102 rejection and respectfully request that it be withdrawn and reconsidered. Applicants respectfully submit that claims 24, 25, 29-35, 40, 41, 46-47, 68-73 and 80 are in a form for immediate allowance.

## **VI. Claim Rejections Under 35 U.S.C. § 103**

A. Claims 10, 11, 15, 18-23, 38, 39, 44, 45, 48, 54-62, 67 and 78 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Pruitt in view of U.S. Patent No. 6,897,020 (hereinafter Link, of record). The Examiner writes that Pruitt discloses the method of 3'



identification as described above and discloses that the 3' identification as described above and discloses that the 5' end of the exon can also be examined for sequence tags (see Figure 1A and paragraphs 40, 43, and 61). The Examiner writes that Pruitt does not disclose the steps in the method where a terminal transferase is used prior to cleavage and amplification. The Examiner writes that Link discloses 5' SAVI where terminal transferase is used to extend the 5' end of the exon after cleavage (see Figure 17; col. 7, line 37-col. 8, line 6; and col. 31). The Examiner writes that one would have been motivated to use terminal transferase as taught by Link in the 5' analysis method of Pruitt because this provides an alternative to linker ligation which requires randomized nucleotides to hybridize with the unknown cohesive end produced by the type IIs enzyme. The Examiner writes that this allows for a straightforward standardization of the protocol and therefore it would have been obvious to one of ordinary skill in the art to use a terminal transferase as taught by Link in the sequence tag identification method of Pruitt with a reasonable expectation of success.

Applicants disagree. However, in order to expedite prosecution, claims 48, 54-62 and 67 have been canceled. Applicants submit that a *prima facie* case of obviousness has not been made with respect to claims 10, 11, 15, 18-23, 38, 39, 44, 45, and 78 because neither Pruitt nor Link, alone or combined, teach all the elements of the present invention. Independent claims 10, 38, 70, 72, and 78 recite a marker exon or marker fragment comprising two restriction enzyme recognition (RER) sites located at the 5' end and/or 3' end of the marker exon or fragment, where the RER sites are different from each other and one of the RER sites is recognized by a Type IIS restriction enzyme so that a Type IIS restriction enzyme will cut the DNA upstream of the 5' end and/or downstream of the 3' end of the marker exon or fragment. The present inventors teach that once the exon marker is integrated into the cellular genome an mRNA containing the marker

exon is produced. The mRNA is ultimately reverse transcribed into cDNA and subjected to digestion with a Type IIS restriction enzyme (or enzymes) that recognize and cleave each of the first and second Type IIS RER sites located at each end of the marker exon, thereby producing a cDNA fragment that includes the marker exon and portions of the upstream and downstream cellular exon sequences (exon tags). Published Specification, at paragraph 74. The third and fourth restriction enzyme recognition sites in the marker exon allow for the marker exon to be cleaved out of amplified cDNA, facilitating the isolation of the exon tags. Published Specification, at paragraph 78.

In contrast, Pruitt teaches at paragraph 43 that the inclusion of a reporter or selection sequence is optional. Furthermore, Pruitt does not teach a marker sequence containing at least two restriction enzyme recognition (RER) sites, where one is a Type IIS restriction enzyme recognition (RER) site. Rather, Pruitt teaches in Figure 1A, restriction enzyme recognition sequences located outside of the marker sequence. Link does not overcome the deficiencies in Pruitt. None of these references teaches or suggest a marker exon or marker fragment comprising two restriction enzyme recognition (RER) sites located at the 5' end and/or 3' end of the marker exon or fragment, where the RER sites are different from each other and at least one of the RER sites is recognized by a Type IIS restriction enzyme so that a Type IIS restriction enzyme will cut the DNA upstream of the 5' end and/or downstream of the 3' end of the marker exon or fragment. Applicants respectfully request that since the references do not teach or suggest all the limitations of the claims that this rejection be withdrawn.

Applicants submit that there is no suggestion or motivation in the cited art to modify or supplement the primary reference Pruitt and thus a prima facie case of obviousness has not been made. There are three possible sources for a motivation to combine a reference – the nature of

the problem to be solved, the teachings of prior art, and the knowledge of one of ordinary skill in the art. MPEP § 2143.01. The level of skill in the art cannot be relied upon to provide the suggestion to combine references. Al-Site Corp. v VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Pruitt's method involves a method for rapid identification of sites of insertion of DNA in to a cellular chromosome. Pruitt does not teach or suggest any remaining problems or shortcomings with their method of gene trapping. Thus, Pruitt does not teach or suggest modifying their method for identifying sequences located at the 5' end of a splice acceptor site.

The teachings of Link do not teach or suggest any problem to be solved or any defects or shortcomings with the method for identifying genes as described in Pruitt. The teachings of Pruitt and Link do not teach or suggest a need to modify or supplement the way 5' sequence tags are obtained and identified. Accordingly, there is no explicit teaching, suggestion or motivation to combine Pruitt with Link.

In addition, there is no implicit teaching as the test for an implicit teaching is what the combined teachings, knowledge of one skilled in the art, and the nature of problem to be solved as a whole would have suggested to one skilled in the art. In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). There are no combined teachings that teach or suggest a reason to modify the methods of Pruitt. There are no teachings, suggestions, or motivations that there is any defect or shortcomings to be solved in Pruitt. One skilled in the art would not have combined Link with Pruitt without the benefit of the teachings of the instant specification. Therefore, there is no implicit teaching, suggestion or motivation to combine Pruitt with Link. Since no explicit or implicit teaching, suggestion or motivation to combine Pruitt with Link exists, Applicants submit that the present invention was reconstructed using hindsight.

Motivation to combine the references requires that the combination sought to be made be desirable not just feasible. Winner International Royalty Corp v Want, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000). Applicants respectfully submit that there is no motivation to modify or supplement Pruitt, either explicitly or implicitly, or that Pruitt states that a problem with its method is unresolved. Thus, a prima facie case of obviousness has not been made and Applicants respectfully request that this rejection be withdrawn. Applicants respectfully submit that claims 10, 11, 15, 18-23, 38, 39, 44, 45, and 78 are in a form for immediate allowance.

B. Claims 10, 11, 15, 18-25, 29-35, 28-41, 44-73, 78, and 80 stand rejected under 35 U.S.C. § 103(a) as being obvious over Link in view of Pruitt.

Applicants submit that Link does not qualify as a reference under 35 U.S.C. §103(c) because the present application and the Link '020 patent were, at the time the invention of the instant application was made, both owned by NewLink Genetics. Submitted herewith for the Examiner's consideration are the relevant assignment documents. Applicants respectfully request that the rejection to claims 10, 11, 15, 18-25, 29-35, 28-41, 44-73, 78, and 80 under §103 be withdrawn and reconsidered. Applicants respectfully submit that claim 10 is in a form for immediate allowance.

## **VII. Double Patenting**

Claims 10, 11, 15, 18-25, 29-35, 38-41, 78, and 80 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 7, 9, 12, and 18-22 of U.S. Patent No. 6,897,020 in view of Pruitt, as follows: instant claims 10, 24, 38, 40, 78, and 80 over patent claims 4 and 7, instant claims 11, 25, 29, 39 and 41 over patent claim 9, instant claims 15 and 29 over patent claim 20, instant claims 18 and 30 over patent claim 21, instant claims 19, 20, 31, and 32 over patent claim 22, instant claims 21, 22, 33, and 34 over

patent claim 18, and instant claims 23 and 35 over patent claim 12. Claims 10, 11, 15, 18-25, 29-35, 38-41, 78, and 80 are directed to an invention not patentably distinct from claims 4, 7, 9, 12, and 18-22 of commonly assigned Patent No. 6,897,020.

Applicants have provided a terminal disclaimer and Applicants respectfully request that this rejection be withdrawn.

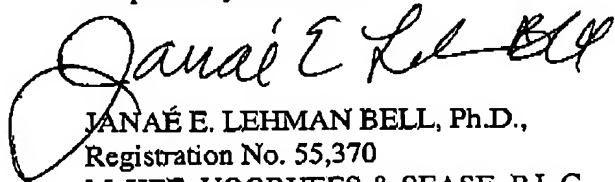
### VIII. Conclusion

Please charge Deposit Account No. 26-0084 for the Terminal Disclaimer attached. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

The Examiner is invited to call the undersigned attorney if he believes that the above amendments do not put the claims in form for immediate allowance.

Respectfully submitted,



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